A concise synthesis of (+)-muscarine

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(+)-Muscarine was synthesized from *S*-(−)-ethyl lactate in five steps with the application of a zinc-mediated allylation reaction in aqueous media. Reversal of chelation-control stereoselectivity was observed in the allylations of chiral α-alkoxy aldehydes in aqueous media.

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Appliquant une réaction d'allylation réalisée en milieu aqueux et faisant intervenir du zinc, on a effectué la synthèse de la (+)-muscarine en cinq étapes à partir du *S*-(−)-lactate d'éthyle. Lors des allylations en milieu aqueux des α-alkoxy aldéhydes chiraux, on a observé un renversement du contrôle de stéréosélectivité de la chélation.

[Traduit par la rédaction]

Introduction

Muscarine (**1**, OH^- instead of I^-) is an alkaloid first isolated from the poisonous mushroom, *Amanita muscaria* (fly agaric) in 1954 (1). Its structure, chemistry and physiological activities have been extensively investigated (2). Muscarine acts as a selective agonist of the neurotransmitter acetylcholine on smooth muscles of the gastrointestinal tract, eye exocrine glands, and heart. As a consequence, the receptor responses in those tissues are termed muscarinic receptors. More recently, with the use of selective antagonists, distinct subtypes of muscarinic receptors were distinguished (3).

Synthesis of muscarine has been accomplished a number of times from different precursors (2–6). Recently, a chemoenzymatic synthesis of muscarine and its stereoisomers has been reported (7). The renewed interest in this molecule is due in part to the recent suggestion that various subtypes of muscarinic receptors may be implicated in Alzheimer disease (8). Because of our interest in this area, we report here an efficient synthesis of (+)-muscarine from the readily available *S*-(−)-ethyl lactate by taking advantage of a zinc-mediated allylation reaction in aqueous media (9, 10).

Results and discussion

S-(−)-Ethyl lactate (**2**) was converted into the 2,6-dichlorobenzyl ether **3** in 90% yield (Scheme 1). DIBAL reduction of **3** gave the aldehyde **4**. Treatment of the crude aldehyde **4** with allyl bromide and zinc powder in water with NH_4Cl as catalyst resulted in a *anti*:*syn* (71:29) mixture of diastereomers **5***a* and **5***b* in 85% combined yield. The two diastereomers were easily separated by flash chromatography (eluent: hexane:ethyl acetate, 20:1). Treatment of **5***a* with iodine in CH_3CN at 0°C gave the cyclized product **6***a* stereospecifically in 85% yield (for previous study of the iodocyclization reaction, see ref. 11). Finally, treatment of **6***a* with excess trimethylamine in ethanol gave (+)-muscarine (2*S*,4*R*,5*S*). A similar reaction sequence with **5***b* gave (+)-epimuscarine **7**. Compared to the previously reported syntheses in the literature, the present synthesis of muscarine offers the advantages of simplicity, good overall yield, and high optical purity of the product from a readily available chiral precursor.[2]

The stereoselectivity in the conversion of **4** and **5** deserves some comments. Normally, the stereoselectivity observed in the addition of *C*-nucleophiles such as organometallic reagents to chiral α-alkoxy aldehydes (and ketones) has been rationalized on the basis of chelation control (12, 13). The carbonyl compound **8** forms the chelate **9** as shown in Scheme 2. The *C*-nucleophile (R^-) attacks from the less-hindered side as indicated by the arrow, giving the chelation-controlled product **10** in preference to the non-chelation product **11** (Scheme 2). The chelation-control approach provides a useful and convenient synthesis of **10**. When this presumed chelation is diminished by the use of a bulky protecting R^2 or by the use of a non-chelating reagent, the non-chelation product **11** can predominate.[3]

Indeed, the reaction of **4** with allylmagnesium bromide in ether afforded the two diastereomers **5***a* and **5***b* in a ratio of 40:60 (*anti*:*syn*) as predicted by the chelation-control model. A similar reaction with diallylzinc in ether (15) resulted in a complicated mixture. The reversal in diastereoselectivity between organic and aqueous media appears to be a general result for several α-alkoxy aldehydes **8***a*, *b*, and *c*. The effects of solvent on diastereoselectivity are summarized in Table 1. We attribute this change to the disruption of chelation in the aqueous media. In support of this, it should be noted that in the case of α-methylphenylacetaldehyde (**12**), where there is no possibility of chelation, there was no significant difference in the diastereoselectivity between allylations in organic or aqueous media (16). However, it is possible that the observed stereoselectivity in the aqueous organometallic-type reactions may be due to factors associated with the metal surface in such heterogenous reactions (10).

The present synthesis of muscarine demonstrates that organometallic-type reactions in aqueous media can make a meaningful contribution to organic synthesis. Further applications of such reactions can be anticipated.

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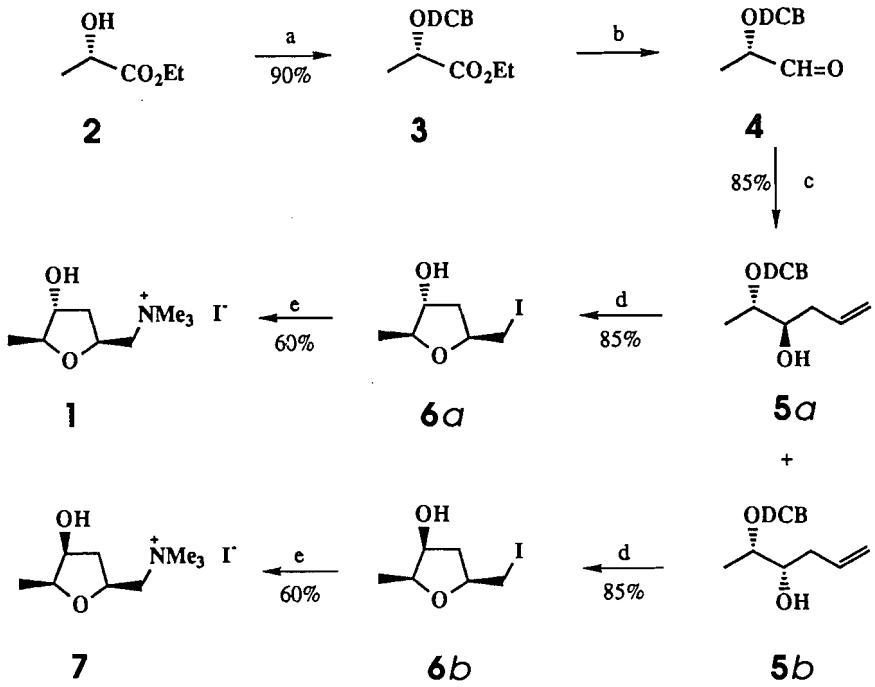
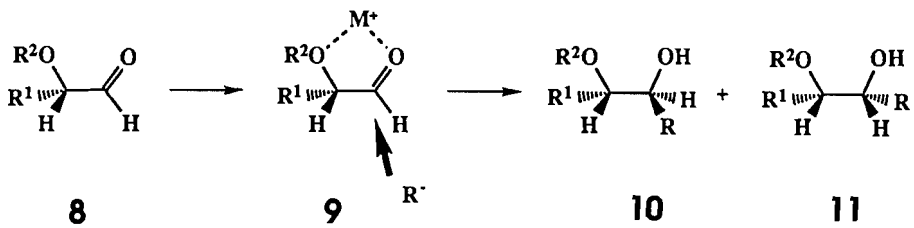
[2]Synthesis of muscarine from lactate ester was not reported previously, presumably because of the difficulty in obtaining the intermediate **5***a* in the conventional organometallic allylation due to chelation control.

[3]Non-chelation-controlled additions can be achieved with alkyltitanium reagents of low Lewis acidity (see ref. 14*a*). For effects of protecting group on chelation control, see ref. 14*b*.



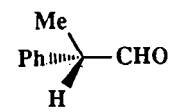
(a) DCBBr/Ag_2O/Et_2O/reflux/6 h; (b) DIBAL-H/Et_2O/-78°C/2 h; (c) CH_2=$CHCH_2Br$/Zn/H_2O/NH_4Cl/3 h; (d) I_2/CH_3CN/0°C/3 h; (e) NMe_3/EtOH/80°C/4 h

SCHEME 1



a: R^1=Ph, R^2=Bn
b: R^1=Bu, R^2=Bn
c: R^1=Me, R^2=Bn

SCHEME 2



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Experimental section

Melting points are uncorrected. Infrared spectra were obtained from films on NaCl plates for liquids and as a KBr pellet for solids on an Analect FTIR AQS-18 spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were recorded on Varian XL-200, XL-300, and Gemini-200 instruments. Mass spectra were determined on a DuPont 21-492B spectrometer. High-resolution mass spectra were obtained on a VG ZAB-HS instrument. Optical rotations were measured on a JASCO DID-140 polarimeter. Column chromatography was performed on silica gel 60 (Merck and EM Science). Acetonitrile was dried by refluxing over CaH_2.

Ethyl (S)-2-(2',6'-dichlorobenzyloxy)-propionate (3)

Dry powdered silver oxide (1.3 g, 5.25 mmol) was added to a solution of ethyl *S*-(−)-lactate (559 mg, 5 mmol) and 2,6-dichlorobenzyl bromide (1.2 g, 5 mmol) in dry ether (50 mL) over a period of 40 min while stirring. The reaction was kept refluxing for 6 h until TLC showed complete disappearance of the starting lactate. Then the reaction mixture was filtered through Celite. Evaporation of the solvent resulted in a crude material, which was purified by flash chromatography (hexane:ethyl acetate, 20:1) to give 1.25 g (90%) of **3** as a colorless oil. IR(neat) *v*: 2986, 2901, 2886, 1746, 1581, 1564, 1436, 1373, 1268, 1197, 1139, 1116, 766 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.30(t, *J* = 7.1, 3H), 1.41(d, *J* = 6.9, 3H), 4.1(q, *J* = 7.1, 1H), 4.2(q, *J* = 7.1, 2H), 4.7(d, *J* = 10.6, 1H), 5.02(d, *J* = 10.61, 1H), 7.25(m, 3H)ppm; HRMS, Exact Mass for $C_{12}H_{14}O_3Cl_2$ + H^+, calcd.: 277.0399; found: 277.0398.

(2S,3R)-2-(2',6'-Dichlorobenzyloxy)-5-hexen-3-ol (5a)

To a solution of the lactate **3** (556 mg, 2 mmol) in ethyl ether (20 mL) under argon, diisobutyl aluminium hydride (2.2 mL,

TABLE 1. Stereoselective allylation of chiral α-substituted aldehydes

Aldehyde	R^1	R^2O	Method[a]	*syn*:*anti*[b]	Combined yield(%)
8*a*	Ph	BnO	O(Mg)	67:33	75
8*a*	Ph	BnO	A(Zn)	43:57	50
8*b*	Bu	BnO	O(Mg)	60:40	60
8*b*	Bu	BnO	A(Zn)	24:76	80
8*c*	Me	BnO	O(Mg)	65:35	50
8*c*	Me	BnO	A(Zn)	35:65	85
4	Me	DCBO	O(Mg)	60:40	45
4	Me	DCBO	A(Zn)	29:71	85
12	Ph	Me	O(Mg)	60:40	90
12	Ph	Me	A(Zn)	68:32	85

[a]For Method, see experimental section.
[b]The ratio of *syn*:*anti* isomers was determined by ^{1}H nmr. See refs. 17 and 21.

1.0 M in hexane) was added dropwise by syringe over 40 min at −78°C. After stirring for 2 h, saturated aqueous ammonium chloride (10 mL) was added to quench the reaction, followed by the addition of 10% HCl (2 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent afforded the crude aldehyde **4**, which was used directly without purification. The crude aldehyde was transferred into a 100-mL flask and mixed with H_2O (50 mL). To the suspension was added allyl bromide (360 mg, 3 mmol) and zinc powder (192 mg, 3 mmol), followed by 1 mL of saturated aqueous ammonium chloride solution to catalyze the reaction. The reaction was continued until no aldehyde could be detected by TLC. The reaction mixture was extracted with ether. The ether extract was dried ($MgSO_4$). Evaporation of the solvent gave a mixture of diastereomers (2–3:1). Separation of the diastereomers was achieved by flash chromatography (hexane:ethyl acetate, 20:1). The major isomer proved to be **5***a*. ^{1}H NMR ($CDCl_3$) δ: 1.21(d, J = 6.3, 3H), 2.21(br, 3H), 3.50(m, 1H), 3.71(m, 1H), 4.75(AB, J = 10.2, 2H), 5.1(m, 2H), 5.8(m, 1H), 7.25(m, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ: 13.9, 36.8, 65.3, 72.2, 77.7, 117.3, 128.3, 129.8, 133.3, 134.9, 136.6 ppm.

*(2S,3S)-2-(2′,6′-Dichlorobenzyloxy)-5-hexen-3-ol (**5**b)*

The minor product from the above reaction proved to be **5***b*. ^{1}H NMR ($CDCl_3$) δ: 1.23(d, J = 6.0, 3H), 2.21(br, 2H), 2.77(d, OH, J = 2.6, 1H), 3.41(m, 2H), 4.80(AB, J = 10.2, 2H), 5.1(m, 2H), 5.8(m, 1H), 7.25(m, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ: 15.2, 37.1, 65.2, 74.2, 77.9, 116.9, 128.3, 129.9, 133.1, 134.6, 136.6 ppm.

*(2S,4R,5S)-2-Iodomethyl-5-methyl-tetrahydrofuran-4-ol (**6**a)*

A solution of **5***a* (266 mg, 0.97 mmol) in acetonitrile (15 mL) was treated with iodine (254 mg, 1.0 mmol) in small portions under an atmosphere of nitrogen at −5°C. After stirring for 3 h at 0°C, the mixture was diluted with ether, and washed with water and 10% sodium thiosulfate aqueous solution. After drying ($MgSO_4$), **6***a* was isolated by flash chromatography (hexane: EtOAc, 2:1) as a colorless oil (234 mg, 85%). IR(neat) ν: 3399(br, OH), 2970, 2930, 1733, 1445, 1358, 1249, 1096, 1063, 984, 992, 905 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.21(d, J = 6.4, 3H), 1.88(m, 1H), 2.0(m, 1H), 2.6(s, br, 1H), 3.25(m, 2H), 3.9–4.2(m, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ: 10.4, 19.7, 40.8, 77.0, 77.2, 83.2 ppm.

*(2S,4S,5S)-2-Iodomethyl-5-methyl-tetrahydrofuran-4-ol (**6**b)*

The compound was obtained from **5***b* by the same procedure as described above as a colorless needle crystal, mp 60–62°C (lit. (11) mp 62°C); IR(KBr) ν: 3435(br, OH), 2885, 1716, 1539, 1179, 1164, 1065, 1039, 1013 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.28(d, J = 6.4, 3H), 1.75(br, 2H), 2.4(m, 1H), 3.35(m, 2H), 3.8–4.0(m, 2H), 4.16(m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ: 79.9, 76.7, 73.4, 41.4, 14.1, 11.8 ppm.

*(+)-Muscarine iodide (**1**)*

The iodoalcohol **6***a* (170 mg, 0.7 mmol) and excess of trimethylamine (~500 mg) were dissolved in 2 mL of ethanol, and heated to 80°C in an ampule for 4 h. On cooling, (+)-muscarine iodide (**1**) crystallized from solution as colorless needles. Recrystallization of the crude material twice from 2-propanol furnished colorless crystals (124 mg, 60%), mp 141–143°C; (lit. (7) mp 138–142°C); $[\alpha]_D^{20}$ +6.3 (*c* 1.0, EtOH) (lit. (7) $[\alpha]_D^{20}$ +6.36 (*c* 0.346, EtOH); IR(KBr) ν: 3374(br, OH), 3016, 2969, 2923, 2906, 2741, 1651, 1486, 1465, 1183, 1100, 1008, 970, 929 cm^{-1}; ^{1}H NMR (D_2O) δ: 1.23(d, J = 6.5, 3H), 2.1(m, 2H), 2.9(br, 1H), 3.25(s, 9H), 3.55(m, 2H), 4.15(m, 2H), 4.65(m, 1H) ppm; ^{13}C NMR (D_2O) δ: 86.9, 78.0, 74.8, 73.4, 56.9, 40.3, 22.0 ppm.

*(+)-Epimuscarine iodide (**7**)*

By the same procedure as described above, (+)-epimuscarine iodide (**7**) was obtained from **6***b* as colorless crystals, mp 169–170°C (lit. (11) mp 175°C); $[\alpha]_D^{20}$ +41.9 (*c* 0.34, EtOH) (lit. (11) $[\alpha]_D^{20}$ +43.23 (*c* 0.636, EtOH); IR(KBr) ν: 3428(br, OH), 2969, 2885, 1653, 1558, 1458, 1065, 1013 cm^{-1}; ^{1}H NMR (D_2O) δ: 1.25(d, J = 6.4, 3H), 1.65(m, 1H), 2.65(m, 1H), 3.20(s, 9H), 3.55(m, 2H), 3.96(m, 1H), 4.25(m, 1H), 4.45(m, 1H) ppm; ^{13}C NMR (D_2O) δ: 83.54, 74.23, 74.04, 73.03, 56.70, 47.55, 16.14 ppm.

Allylation studies

Method O(Mg): To a solution of the aldehyde (1 mmol) in ether (20 mL) at −78°C, allylmagnesium bromide (1 M, 3 mmol) was added dropwise. The mixture was worked up in the usual manner to give the product.

Method A(Zn): A mixture of the aldehyde (1 mmol), allyl bromide (1.5 mmol), and zinc powder (1.5 mmol) in water (20 mL) was stirred at room temperature for 3 h. A few drops of aqueous NH_4Cl was added at the beginning to initiate the reaction. The product was extracted with ether and purified in the usual manner.

*1-Benzyloxy-1-phenyl-5-penten-2-ol (**10**a, **11**a)*

The compound was obtained by Method A(Zn) or Method O(Mg). ^{1}H NMR ($CDCl_3$) δ: (*syn*) 2.05(m, 2H), 2.95(br, 1H), 3.8(m, 1H), 4.2(d, J = 7.7, 1H), 4.35(dd, J = 11.4, 39.3, 2H), 5.0(m, 2H), 5.8(m, 1H), 7.35(m, 10H) ppm; (*anti*) 2.5(m, 2H), 3.9(m, 1H), 4.3(d, J = 1.2, 1H) ppm. The stereochemistry was deduced from ^{1}H NMR spectra of the diols based on the empirical rule of J(CH-OH, *syn*) > J(CH-OH, *anti*) (17) on comparison with similar compounds (18).

*5-Benzyloxy-1-nonanen-4-ol (**10**b, **11**b)*

The compound was obtained by Method A(Zn) or Method O(Mg). ^{1}H NMR ($CDCl_3$) δ: (*syn*) 0.9(t, 3H), 1.35(br, 4H), 1.6(m, 2H), 2.1(br, 1H), 2.3(m, 2H), 3.3(q, J = 5.4, 1H), 3.65(m, 1H), 4.56(dd, J = 11.3, 21.2, 2H), 5.1(m, 2H), 5.85(m, 1H), 7.35(m, 5H) ppm; (*anti*) 3.4(m, 1H), 3.85(m, 1H), 4.6(br, 2H) ppm (19).

*2-Benzyloxy-5-hexen-3-ol (**10**c, **11**c)*

The compound was obtained by Method A(Zn) or Method O(Mg). ^{1}H NMR ($CDCl_3$) δ: (*syn*) 1.20(d, J = 6.0, 3H), 2.2–2.5(m, 2H), 3.5(m, 2H), 4.6(dd, 2H), 5.15(m, 2H), 5.85(m, 1H), 7.35(m, 5H) ppm; (*anti*) 1.19(d, J = 6.3, 3H), 2.25(m, 2H), 3.5(m, 1H), 3.8(m, 1H) ppm (20).

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1. C. H. Eugster and P. G. Waser. Experientia, **10**, 298 (1954).
2. P. C. Wang and M. M. Joullie. The alkaloids. Vol. XXIII. *Edited by* A. Brossi. Academic Press, New York. 1984. pp. 327–380.
3. R. R. Levine and N. J. M. Birdsdall. Trends Pharmacol. Sci. 10. Suppl. Subtypes Muscarinic Recept. IV. Elsevier, Cambridge. 1989.
4. M. C. Pirrung and C. V. DeAmicis. Tetrahedron Lett. **29**, 159 (1988).
5. J. Adams, M. A. Poupart, and L. Grenier. Tetrahedron Lett. **30**, 1753 (1989).
6. S. Tankano, Y. Iwabuchi, and J. Ogasawara. J. Chem. Soc. Chem. Commun. 1371 (1989).
7. M. D. Amici, C. D. Micheli, G. Molteni, D. Pitre, G. Carrea, S. Riva, S. Spezia, and L. Zetta. J. Org. Chem. **56**, 67 (1991).
8. R. Quirion, I. Aubert, P. A. Lapchak, R. P. Schaum, S. Teolis, S. Gauthier, and D. M. Araujo. *In* Trends Pharmacol. Sci. 10. Suppl. Subtypes Muscarinic Recept. IV. *Edited by* R. R. Levine and N. J. M. Birdsdall. Elsevier, Cambridge. 1989. pp. 80–88.
9. (*a*) K. Uneyama, N. Kamaki, A. Moriya, and S. Torii. J. Org. Chem. **50**, 5396 (1985); (*b*) C. Petrier, J. Einhorn, and J. L. Luche. Tetrahedron Lett. **26**, 1449 (1985); (*c*) C. Petrier and J. L. Luche. J. Org. Chem. **50**, 910 (1985); C. Einhorn and J. L. Luche. J. Organomet. Chem. **322**, 177 (1987); (*d*) S. R. Wilson and M. E. Guazzaroni. J. Org. Chem. **54**, 3087 (1989).
10. T. H. Chan and C. J. Li. Organometallics, **9**, 2649 (1990); C. J. Li and T. H. Chan. Organometallics, **10**, 2548 (1991).
11. S. Rychnovsky and P. A. Bartlett. J. Am. Chem. Soc. **103**, 3963 (1981); R. Amouroux, B. Gerin, and M. Chastrette. Tetrahedron Lett. **23**, 4341 (1982); Tetrahedron, **41**, 5321 (1985); J. Mulzer, A. Angermann, W. Munch, G. Schlichthorl, and A. Hentzschel. Ann. 7 (1987); S. Hatakeyama, K. Sakurai, and S. Takano. Heterocycles, **24**, 633 (1986).
12. D. J. Cram and F. A. Abd Elhafez. J. Am. Chem. Soc. **74**, 5828 (1952).
13. (*a*) M. T. Reetz. Angew. Chem. Int. Ed. Engl. **23**, 556 (1984); (*b*) C. H. Heathcock, S. I. Kiyooka, and T. A. Blumenkopf. J. Org. Chem. **49**, 4214 (1984); M. M. Midland and R. W. Koops. J. Org. Chem. **55**, 5058 (1990).
14. (*a*) B. Weidmann and D. Seebach. Angew. Chem. Int. Ed. Engl. **22**, 31 (1983); M. T. Reetz. Chem. Ind. (London), 541 (1981); (*b*) G. E. Keck, W. J. Hehre, and S. D. Kahn. Tetrahedron Lett. **28**, 279 (1987).
15. H. Nagaoka and Y. Kishi. Tetrahedron, **37**, 3873 (1981).
16. T. Kunz and H-U. Reizig. Liebigs Ann. Chem. 891 (1989).
17. M. Fujita and T. Hiyama. J. Am. Chem. Soc. **106**, 4629 (1984).
18. M. Asami and R. Kimura. Chem. Lett. 1221 (1985).
19. G. E. Keck and E. P. Boden. Tetrahedron Lett. **25**, 1879 (1982).
20. M. T. Reetz, K. Kesseler, S. Schmidtberger, B. Wenderoth, and R. Steinbach. Angew. Chem. Int. Ed. Engl. **22**, 989 (1983).
21. R. E. Ireland, S. Thaisrivongs, and P. H. Dussault. J. Am. Chem. Soc. **110**, 5768 (1980); W. C. Still and J. A. Schneider. Tetrahedron Lett. **21**, 1035 (1980); J. A. Marshall and G. P. Luke. J. Org. Chem. **56**, 483 (1981).